Questions

icodextrin
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Cardio-Renal Advisory Committee is asked to give advice on the benefits and risks of Extraneal, a dialysis solution for use in peritoneal dialysis in patients with end-stage renal disease. The NDA database includes 493 patients exposed to Extraneal who were followed for a mean duration for 232 days, compared to 347 patients exposed to dialysis solutions containing dextrose for a mean duration of 203 days. This represents the largest database submitted in support of a peritoneal dialysis solution application to date. Reviews of biopharmaceutics and chemistry present no apparent barriers to its approval.

1. Do the results of the clinical trials establish that Extraneal is an effective peritoneal dialysis solution?

2. The sponsor has submitted data suggesting that Extraneal is more effective in removing water ('ultrafiltration') and in removing waste products ('creatinine and urea clearance') than the 1.25% and 2.5% dextrose-containing dialysis solutions, but not the 4.25% dextrose-containing dialysis solution.
   2.1 If Extraneal were to be approved, are these data sufficient to support a claim of superior efficacy to existing dextrose-based dialysis solutions?
      2.1.1 If so, please describe the clinical relevance of these effects (that is, how do they make a user 'feel better or live longer') and suggest language describing these findings in the label.
      2.1.2 If not, what might be required for a dialysis solution to claim superior efficacy to an existing approved product?

3. In study RE-97-CA131, the sponsor measured changes in patients' symptoms using three different instruments: the Kidney Disease Quality of Life (KDQoL), Short-Form 36 (SF-36), and the Global assessment of QoL.
   3.1 From these data, what can you conclude about the effects of Extraneal on symptoms compared to dextrose-containing dialysis solutions?

4. Icodextran is absorbed systemically.
   4.1 Are the data on the absorption, distribution and metabolism of icodextran sufficient to:
      4.1.1 Describe them in labeling?
      4.1.2 Explain any pharmacodynamic or clinical effects that might be of concern?

5. Are there sufficient data to conclude that Extraneal is a "safe" peritoneal dialysis solution with respect to:
   5.1 Mortality?
      5.1.1. If not, what assurance would you think appropriate?
      5.1.2. Is this a major factor that would bar approval, or is it simply a labeling issue?
   5.2 Adverse skin reactions?
      5.2.1 If not, what assurance would you think appropriate?
      5.2.2 Is this a major factor that would bar approval, or is it simply a labeling issue?
   5.3 Peritonitis?
      5.3.1 If not, what assurance would you think appropriate?
      5.3.2 Is this a major factor that would bar approval, or is it simply a labeling issue?
   5.4 Loss of membrane permeability?
      5.4.1 If not, what assurance would you think appropriate?
      5.4.2 Is this a major factor that would bar approval, or is it simply a labeling issue?
   5.5 Other adverse reactions not listed above?

6. Should Extraneal be approved as a peritoneal dialysis solution?
   6.1 If so, should labeling describe Extraneal as:
      6.1.1 a dialysate similar in safety and efficacy to other dialysis solutions?
      6.1.2 an alternative dialysis solution, to be used under specific circumstances? If so, is that limitation for the use of Extraneal based on its enhanced efficacy under specific circumstances (*e.g.*, need for enhanced ultrafiltration), or is it based on increased safety concerns (*e.g.*, use only when dextrose-containing dialysis solutions have 'failed')?